REMARKS

Applicants note that the Amendment filed on September 26, 2003 has been acknowledged and entered into the record. Upon entry of the present amendment, claims 9, 12-15 and 17-20 are pending. Claim 9 has been amended herein, and support for the amendment to claim 9 is found throughout the specification as originally filed. For example, support is found at least at page 6, lines 5-24. Accordingly, no new matter has been added.

Claim Rejections Maintained 35 U.S.C. § 103

The Examiner has maintained the rejection of claims 9, 12-15 and 17-20 under 35 U.S.C. § 103(a) as obvious over WO 99/54445 to Joshi *et al.* ("Joshi") in view of O'Leary, Sheibani and Streit (each of which was cited in the previous Office Actions). On page 2 of the Office Action, the Examiner states:

> Although Joshi *et al.* teaches the method of using genes and DNA topoisomerase inhibitors, one of ordinary skill in the art would have found it obvious to use polypeptides in place of the nucleic acid molecules [as] both Sheibani *et al.* and Streit *et al.* taught that the protein form of TSP was effective in treating angiogenic conditions in vivo. Furthermore, O'Leary *et al.* taught that the combination of an angiogenic inhibitor in combination with camptothecin, a DNA topoisomerase inhibitor, was effective in initiating an anti-tumor response.

According to the Examiner, it would have been *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose, as "the idea of combining them flows logically from their having been individually taught in the prior art." (Office Action, page 3).

Applicants believe that the Examiner has failed to establish a *prima facie* case of obviousness. According to MPEP 2143:

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Claim 9 has been amended to recite a method of inhibiting tumor cell growth in a mammal by administering a composition that includes a thrombospondin polypeptide and an inhibitor of DNA topoisomerase I enzyme activity, wherein the tumor cell is a colon tumor cell, wherein the thrombospondin polypeptide is thrombospondin-1 (TSP-1) or thrombospondin-2 (TSP-2) and the inhibitor of DNA topoisomerase I enzyme activity is a water soluble camptothecin compound, and wherein administering the composition produces a synergistic antineoplastic effect in the mammal such that tumor growth is inhibited in the presence of the thrombospondin polypeptide and said water soluble camptothecin compound compared to in the absence of said thrombospondin polypeptide and said water soluble camptothecin compound.

Thus, the methods of the claimed invention are directed to methods of administering a TSP polypeptide and a water-soluble camptothecin compound in combination to produce a synergistic antineoplastic effect in a mammal.

Joshi, in contrast, fails to describe or suggest such methods that produce a synergistic antineoplastic effect in a mammal. In particular, Joshi describes methods of transforming a target cell with a therapeutic nucleic acid delivered to the cell by administering a nucleic acid encoding an anti-angiogenic compound and a cell-cycle blocker compound. There is no teaching or suggestion in this reference of delivering a thrombospondin polypeptide and a cell-cycle blocker such as camptothecin. Contrary to the Examiner's assertion, one of ordinary skill in the art would not have been motivated by the Joshi reference to use a thrombospondin polypeptide in place of a nucleic acid in the methods and compositions described therein.

As described throughout the Joshi reference, the cell-cycle blocker compound is administered to synchronize target cells "at a stage in the cell cycle when the nuclear membrane is substantially dissolved" for the purpose of hastening translocation of the nucleic acid to the cell nucleus. (*See e.g.*, Joshi at page 9, lines 20-23). Thus, Joshi describes the cell cycle blocker compound specifically for administration with a nucleic acid, not a polypeptide. Those skilled in the art would appreciate that thrombospondin polypeptides, such as TSP-1 and TSP-2, do not require solubilizing the nuclear membrane to inhibit angiogenesis, nor do they require translocation to the cell nucleus for activity. Thrombospondin polypeptides are extracellular matrix proteins that function by modulating cell-to-cell phenomena (*e.g.*, extracellular signaling mechanisms). Thus, thrombospondin polypeptides remain outside of the cell. Therefore, if, as

the Examiner asserts, one of ordinary skill in the art would have found it obvious to use thrombospondin polypeptides in place of the nucleic acid molecules in the Joshi methods, there would be no motivation to co-administer a cell-cycle blocker compound, as there would no longer be a need to solubilize the nuclear membrane. Thus, there is no suggestion or motivation to modify the Joshi methods and compositions to include a thrombospondin polypeptide.

Moreover, even if thrombospondin polypeptides were used in the Joshi methods, one of ordinary skill in the art would have no reasonable expectation that the administration of a composition that contains a TSP polypeptide and a DNA topoisomerase inhibitor would successfully produce a synergistic antineoplastic effect when administered to a mammal. It is generally known any potential drug or therapeutic composition contemplated for *in vivo* use is first tested in an *in vitro* experimental model such as animal or human cells. For example, before a pharmaceutical company (or other research entity) can initiate clinical trial testing in humans, it must conduct extensive preclinical laboratory research. Thus, a skilled artisan investigating the therapeutic effect(s) of administering a composition containing a TSP polypeptide and a DNA topoisomerase inhibitor would first evaluate the composition in an *in vitro* model. However, as described in the instant specification at page 6, lines 2-4, a composition containing a TSP polypeptide and a DNA topoisomerase inhibitor does not produce enhanced tumor cell cytotoxicity *in vitro* in cultures of the human colon tumor cell line HT29. It was surprising, indeed, to observe inhibition of tumors *in vivo*.

In light of these *in vitro* results, those of ordinary skill in the art would not reasonably expect that administering the TSP polypeptide and DNA topoisomerase inhibitor to a mammal would produce any meaningful effect on tumor cell cytotoxicity, let alone a synergistic antineoplastic effect in that animal. Applicants were the first to show the surprising effect that the administration of a TSP polypeptide and a DNA topoisomerase inhibitor produces enhanced tumor cell cytotoxicity. Therefore, any suggestion that it would have been obvious to administer a TSP polypeptide and a DNA topoisomerase inhibitor to a mammal to produce a synergistic effect on tumor cell cytotoxicity is an improper application of hindsight.

The surprising synergistic antineoplastic effect is an important advantage over other methods of inhibiting tumor cell growth, as the methods and compositions of the claimed invention require smaller amounts of thrombospondin and camptothecin, which is known to be a

toxic compound. However, Joshi fails to describe or suggest methods that produce a synergistic antineoplastic effect, and, therefore, use smaller dosages of thrombospondin and camptothecin. Thus, Joshi fails to describe or suggest every element of the claimed invention.

Accordingly, Joshi fails to describe or suggest every element of the claimed methods. As such, amended claim 9 and its dependent claims (including claims 12-15 and 17-20) are not obvious over this reference.

The addition of the O'Leary, Streit and Sheibani references, either alone or in combination, fail to remedy the deficiencies in the teachings of Joshi, as none of these references describe or suggest a method of inhibiting colon tumor cell growth by administering a combination of a thrombospondin polypeptide and a water-soluble camptothecin compound to produce a synergistic antineoplastic effect in a mammal. As described above, the Joshi reference would not motivate one of ordinary skill in the art to use a thrombospondin polypeptide and a cell-cycle blocker compound such as camptothecin. Therefore, those skilled in the art would not be motivated to combine the teachings of O'Leary, Streit and/or Sheibani with the methods and compositions described in the Joshi reference. Accordingly, claims 9, 12-15 and 17-20 are not obvious over these references, and Applicants request that the Examiner withdraw this rejection.

New Claim Rejections Under 35 U.S.C. § 102

The Examiner has rejected claims 9, 12 and 17-20 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,406,693 to Thorpe *et al.* ("Thorpe"). In particular, the Examiner has asserted that Thorpe describes "a method of treating colon cancer in a human with a composition that comprises camptothecin (*see* Thorpe, col. 72) and a TSP, specifically TSP-1 (*see* Thorpe, col. 79)." (Office Action, page 4).

As described above, the pending claims have been amended herein to recite a method of inhibiting tumor cell growth in a mammal by administering a composition that includes a thrombospondin polypeptide and an inhibitor of DNA topoisomerase I enzyme activity, wherein the tumor cell is a colon tumor cell, wherein the thrombospondin polypeptide is thrombospondin-1 (TSP-1) or thrombospondin-2 (TSP-2) and the inhibitor of DNA topoisomerase I enzyme activity is a water soluble camptothecin compound, and wherein administering the composition produces a synergistic antineoplastic effect in the mammal such that tumor growth is inhibited in

the presence of the thrombospondin polypeptide and said water soluble camptothecin compound compared to in the absence of said thrombospondin polypeptide and said water soluble camptothecin compound.

Thus, the methods of the claimed invention are directed to methods of administering a TSP polypeptide and a water-soluble camptothecin compound in combination to produce a synergistic antineoplastic effect in a mammal.

Thorpe, in contrast, fails to describe such methods of producing a synergistic antineoplastic effect. As described throughout Thorpe, the methods and compositions require at least a first antibody, or antigen-binding region thereof, that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells. Thorpe does not describe or suggest any compositions that do not include an antibody (or antibody-conjugate) that binds to an aminophospholipid. In fact, Thorpe fails to even describe or suggest a composition that contains an antibody that binds to an aminophospholipid, thrombospondin and camptothecin – the Thorpe compositions include either the antibody and thrombospondin or the antibody and camptothecin.

Furthermore, Thorpe fails to describe the use of a water-soluble camptothecin compound, as required by the claimed invention. Thorpe simply lists camptothecin as a known chemotherapeutic agent. Naturally occurring camptothecin is known to have poor water solubility and, therefore, must be dissolved in solvents such as DMSO and sodium hydroxide. (*See e.g.*, catalog product descriptions of commercially available camptothecin solutions, attached hereto as Exhibit A). The water-soluble camptothecin compounds recited by the amended claims, in contrast, do not require the use of such harsh solvents.

Finally, Thorpe fails to describe or suggest methods and compositions for inhibiting tumor cell growth that produce a synergistic antineoplastic effect in a mammal. Thus, Thorpe fails to describe every element of the claimed invention. Amended claims 9, 12 and 17 are, therefore, novel over this reference, and this rejection should be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Ingrid A. Beattie, Reg. No. 42,306
Attorney for Applicant
c/o Mintz, Levin
One Financial Center
Boston, MA 02111
Telephone (617) 542 6000
Fax (617) 542 2241
Customer No: **30623**

TRA 1880869v1